IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA L.P., Plaintiff, v. WATSON LABORATORIES, INC., Defendant.	Civil Action No. 14-1227 (SLR) (SRF)
PURDUE PHARMA L.P., Plaintiff, v. WATSON LABORATORIES, INC., Defendant.	Civil Action No. 14-1410 (SLR) (SRF)
PURDUE PHARMA L.P., Plaintiff, v. ACTAVIS LABORATORIES UT, INC., Defendant.	Civil Action No. 15-192 (SLR) (SRF)

DECLARATION OF RUSSELL OWEN POTTS, PH.D., ON CLAIM CONSTRUCTION

I, Dr. Russell Owen Potts, a citizen of the United States, do declare as follows:

1. I was asked by the law firm Winston & Strawn LLP to provide a declaration addressing the meaning of the term “first order plasma level increase” as it appears in U.S. Patent No. RE 41,408 and RE 41,571.

II. SUMMARY OF OPINION

2. It is my opinion that the claim term "first order plasma level increase" means "plasma concentrations which increase over a specified time period."

3. I understand that Plaintiff proposes the following construction: "plasma concentrations which increase steadily over a specified time period." In my opinion, this construction is not supported by the specification and would be indefinite.

III. PERSONAL BACKGROUND AND QUALIFICATIONS

4. I expect to testify regarding my background, qualifications, and experience related to my opinions expressed in this declaration. Further details are given in my CV, attached as Appendix A.

5. I received my Bachelor of Science degree in Chemistry from Michigan State University in 1968 and my Master's of Science degree in Physical Chemistry from Cornell University in 1970. I earned my Ph.D. in Biochemistry from the University of Massachusetts-Amherst in 1978. I completed my postdoctoral study in Chemistry at Yale University in 1979.

6. I have over thirty years of experience in pharmaceutical research and development, including the research and development of pharmaceutical products for transdermal delivery of active pharmaceutical ingredients. My professional experience includes employment at Pfizer Central Research from 1982 until 1990, where I ultimately served as the Manager of the Dermal Therapeutics Group from 1986 until 1990, and employment at Cygnus Therapeutic Systems from 1990 until 2002, where I ultimately served as the Vice President of Research and Development from 2001 until 2002. Since 2002, I have served as an independent consultant with a special expertise in transdermal pharmaceutical formulations. I have also served on the Board of Directors for Solianis Holding AG, VivoMedical, Inc., Vyteris, Inc., and

FreeLance, Inc. I have also taught from 1992 to 2012 as an Adjunct Professor at the University of California, San Francisco, in the Department of Biopharmaceutical Sciences.

7. I have published numerous articles and book chapters in the area of pharmaceutics and transdermal drug delivery. I have served on the Editorial Board or Scientific Advisory Board of many scientific publications. I also belong to several professional societies for pharmaceutical science and technology, including the American Association of Pharmaceutical Sciences. I am a Fellow of the American Association of Pharmaceutical Sciences and the American Institute of Biological and Medical Engineering. I have received multiple grants for my scientific research, including grants from the National Institutes of Health. I am a named inventor on 35 issued U.S. Patents.

IV. MATERIALS CONSIDERED IN FORMING MY OPINIONS

8. I have reviewed Purdue's Opening Brief on Claim Construction, the Declaration of Lawrence Fleckenstein, and the materials cited therein (including the documents attached to the Declaration of Sarah Geers). I have also reviewed the RE 41,408 patent, the RE 41,571 patent, the RE 41,489 patent, and their respective file histories.

9. I have also reviewed the materials cited in this declaration.

10. For purposes of claim construction only, I accept the definition of the level of skill of the person having ordinary skill in the art ("POSA") offered by Dr. Fleckenstein. (Fleckenstein Decl. ¶ 13.)

V. LEGAL STANDARDS

11. While I am neither a patent lawyer nor an expert in patent law, I have been informed of the applicable legal standards of claim construction. I have relied upon these legal standards, as explained to me by counsel, in forming my opinions set forth in this declaration.

12. I was asked to form opinions based on the perspective of a POSA. I understand that a POSA is a hypothetical person considered to have normal skills, knowledge, and education in the field to which the asserted patent relates at the time the invention was made.

13. I understand that claims are construed as they would have been understood by a POSA, and that courts may consider the claim language, the specification, the prosecution history, and relevant extrinsic evidence.

14. I understand that the "intrinsic evidence" includes the specification, claims, and prosecution history.

15. I understand that a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.

VI. BRIEF BACKGROUND ON PHARMACOKINETICS

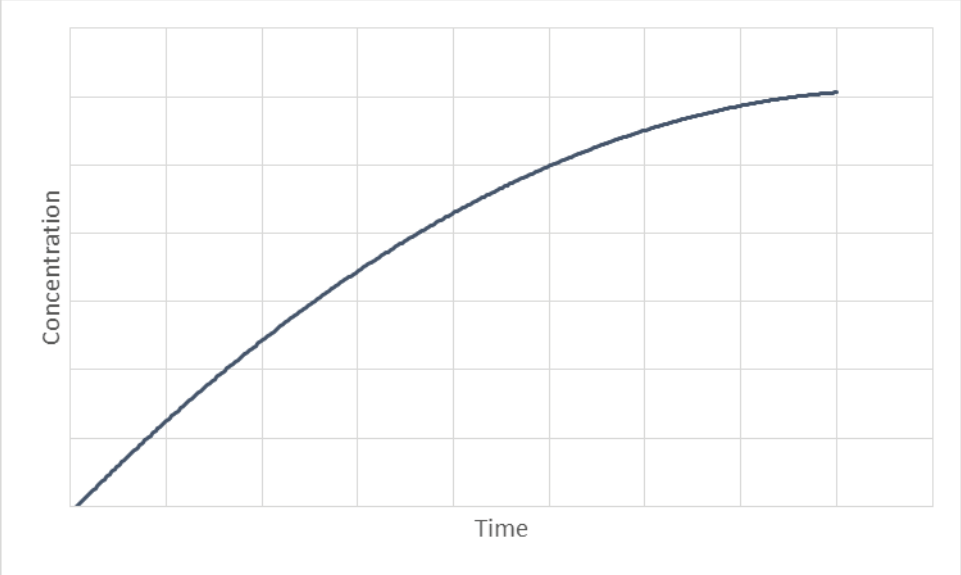
16. I agree with Dr. Fleckenstein that a POSA would have understood that "blood plasma profiles are affected by the rate of drug absorption and elimination." However, in real-world application with actual patients, blood concentration level of a drug and rates of absorption do not precisely follow mathematical models. I agree with Dr. Fleckenstein that in general, first-order absorption means that the rate of drug absorption depends on and is proportional to the concentration of the drug available. My proposed definition "plasma concentrations which increase over a specified time period" captures this concept, while Dr. Fleckenstein's proposal does not provide a standard that can be objectively applied.

17. According to the textbook *Applied Biopharmaceutics & Pharmacokinetics*, cited by Dr. Fleckenstein, a first-order absorption model is a model where the *rate of absorption* is defined by:

$$\frac{dD_{GI}}{dt} = -k_a D_{GI}$$

where k_a is a constant and D_{GI} is "the amount of drug in the GI tract at any time." (JA208.) In this equation, the *rate* of absorption *decreases* over time because the amount of drug in the transdermal delivery system decreases as absorption occurs. However, this is an idealized, theoretical representation of drug absorption during transdermal drug delivery. As shown below, real-world data from patients never actually fits this model.

18. A mathematically modeled graph of plasma concentrations against time for first-order absorption, as defined by the equation above, would look like this:



Because the rate is constantly decreasing, plasma concentration is increasing, but not steadily.

19. Rather than offer this equation as his definition of "first order," Dr. Fleckenstein offers a quite different construction: a "stead[y]" increase. As I will explain below, it is my opinion that this construction would be indefinite.

20. I believe the reason Dr. Fleckenstein does not justify this equation as his definition of "first order" is that this equation will never be met when a transdermal patch is applied to an actual patient. For example, the data reflected in Figure 1 does not conform to this equation. Dr. Fleckenstein did not attempt to apply this equation to the data reflected in Figure 1 or any other data from the specification.

VII. "FIRST ORDER PLASMA LEVEL INCREASE" REFERS TO PLASMA CONCENTRATIONS THAT INCREASE OVER A SPECIFIED TIME PERIOD

21. The only claim term in dispute is "first order plasma level increase." In my opinion, this phrase refers to an increase in plasma concentrations over a specified time. This construction excludes, for instance, an immediate sharp increase (sometimes called a "step" increase) sometimes seen in other dosage forms.

A. The Asserted Claims

22. The term "first order plasma level increase" appears in three independent claims of the RE 41,408 patent. Those claims provide:

> 10. A method of treating pain in a human patient comprising:
>
> administering an opioid transdermally to said human patient by applying a transdermal delivery system comprising an opioid to the skin of a patient, and maintaining said transdermal delivery system in contact with the skin of said patient for [at least 5] 7 days, said transdermal delivery system providing a ***substantially first order plasma level increase of said opioid from the initiation of the dosing interval until about 72 hours after the initiation of the dosing interval*** and providing a substantially zero order plasma level fluctuation of said opioid from about 72 hours after the initiation of the dosing interval until the end of [at least] the [five] seven-day dosing interval.
>
> 20. A method of treating pain in a human patient comprising:
>
> transdermally administering an active ingredient, wherein the active ingredient consists essentially of an opioid, to said human patient by applying a transdermal delivery system comprising an active ingredient, wherein the active ingredient consists essentially

> of an opioid to the skin of a patient, and maintaining said transdermal delivery system in contact with the skin of a patient for 7 days, said transdermal delivery system providing ***a substantially first order plasma level increase of said opioid from the initiation of the dosing interval until about 72 hours after the initiation of the dosing interval*** and providing a substantially zero order plasma level fluctuation of said opioid from about 72 hours after the initiation of the dosing interval until the end of the seven-day dosing interval.
>
> 22. A method of treating pain in a human patient comprising transdermally administering an active ingredient, wherein the active ingredient consists of an opioid, to said human patient by applying a transdermal delivery system comprising an active ingredient, wherein the active ingredient consists of an opioid to the skin of a patient, and maintaining said transdermal delivery system in contact with the skin of said patient for 7 days, said transdermal delivery system ***providing a substantially first order plasma level increase of said opioid from the initiation of the dosing interval until about 72 hours after the initiation of the dosing interval*** and providing a substantially zero order plasma level fluctuation of said opioid from about 2 hours after the initiation of the dosing interval until the end of the seven-day dosing interval.

(emphasis added).

23. The term "first order plasma level increase" is also used—in the same way—in several claims of the RE 41,571 patent.[1] Claim 1 is representative:

> 1. A method of treating pain in a human patient, comprising
>
> administering buprenorphine transdermally to said human patient by applying a transdermal delivery system to the skin of a patient, and maintaining said transdermal delivery system in contact with the patient's skin for [at least 5 days] a seven day dosing interval, said transdermal delivery system maintaining a mean relative release rate of from about 3 ug/hr to about 86 ug/hr and ***providing a substantially first order plasma level increase*** of buprenorphine from the initiation of the dosing interval until about 72 hours after the initiation of the dosing interval; and a mean relative release rate of about 0.3 ug/hr to about 9 ug/hr and providing a substantially zero order plasma level fluctuation of buprenorphine from about 72 hours after the initiation of the dosing interval until the end

[1] Since the patents-in-suit share the same specification, I cite only to the RE '408 patent.

> of[at least] the [five] seven-day dosing interval, such that the following mean plasma concentrations are achieved:
>
> a mean plasma concentration from about 0.3 to about 113 pg/ml at about 6 hours after initiation of the dosing interval;
>
> a mean plasma concentration from about 3 to about 296 pg/ml at about 12 hours after initiation of the dosing 40 interval;
>
> a mean plasma concentration from about 7 to about 644 pg/ml at about 24 hours after initiation of the dosing interval;
>
> a mean plasma concentration from about 13 to about 45 753 pg/ml at about 36 hours after initiation of the dosing interval;
>
> a mean plasma concentration from about 16 to about 984 pg/ml at about 48 hours after initiation of the dosing interval;
>
> a mean plasma concentration from about 20 to about 984 pg/ml at about 60 hours after initiation of the dosing interval;
>
> a mean plasma concentration from about 21 to about 1052 pg/ml at about 72 hours after initiation of the 55 dosing interval;
>
> [and a mean plasma concentration from about 19 to about 1052 pg/ml over at least the next 48 hours]
>
> a mean plasma concentration from about 23 to about 1052 pg/ml at about 96 hours after initiation of the dosing interval;
>
> a mean plasma concentration from about 23 to about 1052 pg/ml at about 120 hours after initiation of the dosing interval;
>
> a mean plasma concentration from about 22 to about 65 970 pg/ml at about 144 hours after initiation of the dosing interval; and
>
> a mean plasma concentration from about 19 to about 841 pg/ml at about 168 hours after initiation of the dosing interval.

(emphasis added)

B. The meaning of "increase over time"

24. A POSA would understand that a "first order plasma level increase" must refer to plasma concentrations which increase over a specified time period. The term ***excludes*** an

instantaneous, stepwise increase, such as that described in Comparative Example B of the patents-in-suit.

25. The patents describe three "Comparative Examples," A-C, that were tested in a clinical study. (JA40-42, RE '408 patent, 27:12-31:42.) This study compared a single application transdermal patch (akin to the alleged invention), an intravenous injection, and three sequential applications of the patch.

26. The single application patch produced blood plasma concentrations that increased over 72 hours, as the below Table 5 shows. However, it must be noted that the reported blood plasma concentrations do not increase at a steady rate and do not increase between each of the individual time periods reported from 2 to 72 hours (for example, the period from 24 to 30 hours and the period from 48 to 60 hours show decreases in mean blood plasma concentrations).

TABLE 5

Comparative Example A

HOUR	MEAN PLASMA CONC. (pg/ml)	STD. DEV	CV %
2	2.04	5.87	287.10
3	7.96	16.28	204.47
4	14.84	18.63	125.51
6	23.49	25.81	109.85
8	42.34	37.91	89.52
10	72.03	71.36	99.07
12	85.96	68.69	79.90
16	133.89	103.43	77.25
24	175.58	120.17	68.44
30	169.15	108.65	64.23
36	200.16	134.45	67.17
48	251.10	156.66	62.39
60	250.11	125.01	49.98
72	286.50	131.58	45.92
78	168.73	61.26	36.30
84	114.68	52.72	45.97
96	90.75	39.12	43.11
108	56.82	25.66	45.17
120	44.85	23.80	53.06
132	30.40	21.87	71.95
144	29.14	20.27	69.58

(JA41, RE '408 patent, 29:5-29.)

27. The intravenous injection, on the other hand, produced a much different increase. Specifically, plasma concentrations increased almost instantly, and peaked after just 1.8 minutes (0.03 hours), as Table 7 shows:

TABLE 7

Comparative Example B

HOUR	MEAN PLASMA CONC. (pg/ml)	STD. DEV	CV %
0.02	14812.04	11319.10	76.42
0.03	31052.04	16156.81	52.03
0.05	24547.00	16461.86	67.06
0.08	6418.80	1976.26	30.79
0.17	3360.76	2457.58	73.13
0.25	1747.96	465.81	26.65
0.33	1210.08	219.28	18.12
0.42	1050.00	242.10	23.06
0.50	931.52	207.25	22.25
0.75	692.92	175.29	25.30
1.00	584.40	148.93	25.48
1.50	457.44	131.44	28.73
2.00	335.12	79.36	23.68
3.00	238.80	63.03	26.39
4.00	170.87	49.84	29.17

(JA41, RE '408 patent, 30:30-50.)

28. In my opinion, a POSA reading the asserted claims in light of the intrinsic record would understand that the patentees, by using the term "first order," were distinguishing their alleged inventions from Comparative Example B. Thus, it would be wrong to say that under my proposed construction, *any* increase is a "first order" increase.

C. My opinion is consistent with the claim language.

29. A POSA would understand "first order" increase to refer to an "increase over a specified time period" in light of the specification and claim language. The claims of the RE '571 patent, which require certain mean plasma concentration levels, describe an increase over time. For instance, claim 1 above permits a maximum concentration of only 296 pg/ml after 12 hours, but allows for a much higher concentration of 1052 pg/ml after 72 hours. This is inconsistent with the stepwise increase described in Example B.

30. Purdue's Opening Claim Construction Brief argues that my proposed construction is redundant and reads "first order" out of the claims. (Purdue Br. 8.) But as I explained above, "increase over a specified time period" excludes the stepwise increase associated with an injection.

D. My opinion is consistent with the specification.

31. The specification supports my opinion in two ways.

32. *First*, the specification supports my opinion that the patentees intended to distinguish the sharp, stepwise increases associated with injection from the increase seen with the patch. The patentees state that one benefit of the invention is that "the large plasma concentration peaks obtained in the prior art, e.g., through intravenous dosing, can be avoided." (JA43, RE '408 patent, 34:61-63.)

33. *Second*, the specification defines "first order" as an increase over time—consistent with my proposed construction. The specification reads:

> The term "first order" pharmacokinetics is defined as plasma concentrations which increase over a specified time period.

(JA29, RE '408 patent, 6:20-22.)

34. In my view, this definition is clear, and it says nothing about "steadily." Further, this passage expressly purports to "define[]" a term.

35. In my opinion, a POSA would understand that "first order" would have the same meaning when that defined term is used to modify "pharmacokinetics" as when it is used to modify "plasma level increase." Plasma concentration changes are a way of measuring pharmacokinetics. Dr. Fleckenstein did not opine otherwise. Indeed, the entire basis of his opinion seems to be rooted in his experience with pharmacokinetics. (Fleckenstein Dec. ¶ 11.) He also draws a "causal link" between first order kinetics and the rising blood plasma concentrations. (Fleckenstein Dec. ¶ 23.)

36. Dr. Fleckenstein claims that a different passage in the specification supports his opinion:

> It is apparent from the pharmacokinetic results obtained with respect to Example 1 that ***the mean blood plasma concentrations rose steadily and peaked*** at about the 3-day time point during the dosing interval . . . . Further, it is apparent from the buprenorphine plasma concentrations ***that first order kinetics were present*** during the first 72 hours of the dosing interval, and substantially zero order kinetics were present thereafter.

(JA39, RE '408 patent, 25:63-26:8 (emphasis added).)

37. In my view, this passage cannot bear the weight Dr. Fleckenstein assigns to it. First, it does not purport to *define* anything, or to *limit* "first order" to a "steady" increase. Rather, this passage merely asserts that: (i) Example 1 can be described as a "stead[y]" increase, and (ii) Example 1 displays "first order kinetics."

38. Further, as I will explain more fully below, the word "steadily" is vague, and its use would render the asserted claims indefinite. The term does not function as a claim limitation.

39. Finally, Purdue's Opening Brief on Claim Construction argues that the term "substantially first order" is defined "in the specification and/or via the examples." (Purdue Br.

12.) But Purdue does not explain *which* example supports Dr. Fleckenstein's opinion. As I will explain below, Figure 1 of the patents does not describe a "steady" increase.

E. My opinion is consistent with the prosecution history.

40. I have reviewed the prosecution histories of the patents-in-suit. I am not aware of anything in the prosecution history that contradicts my opinion.

41. Purdue's Opening Claim Construction Brief argues that Dr. Fleckenstein's construction is supported by the prosecution history because the patentees distinguished two prior art references, which allegedly did not disclose a "first order rate of increase." (Purdue Br. 11.) This argument assumes what it seeks to prove: the *meaning* of "first order." Because a construction of "increase over time" gives meaning to the term, and Dr. Fleckenstein's proposed construction does not, my construction is consistent with the prosecution history.

VIII. DR. FLECKENSTEIN'S PROPOSED CONSTRUCTION IS INDEFINITE.

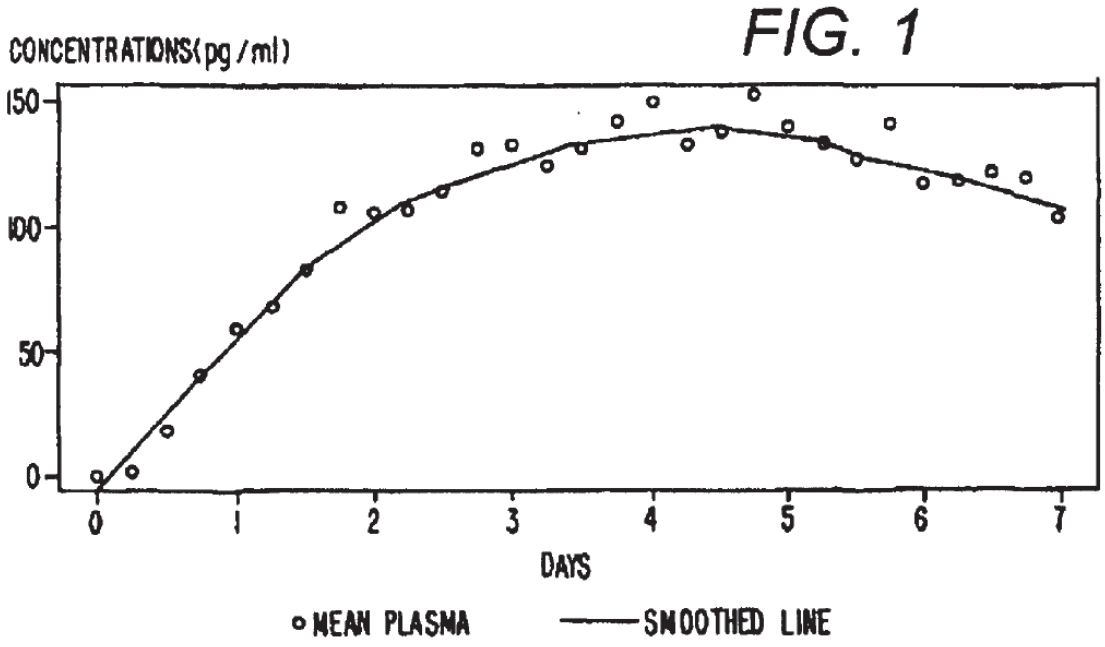
42. Dr. Fleckenstein argues that "first order increase" should be construed to refer to plasma levels that increase "steadily" over time. But in my opinion, a POSA would not be able to discern the meaning of "steadily." As I understand the law, that inability to discern the meaning of "steadily" means any claims that contain this term would be indefinite.

A. Dr. Fleckenstein's proposed construction is internally inconsistent and impossibly vague.

43. Although Dr. Fleckenstein purports to define a "first order" plasma increase as "steadily increasing blood plasma levels," he actually defines this construction in at least four different ways.

44. First, he suggests that Figure 1 of the patents-in-suit depicts "steadily increasing blood plasma concentrations" (Fleckenstein Decl. ¶ 23). I note that in the figure below, the

"smooth line" does not actually represent the data; it merely approximates the data. Rather, the points represent the actual data:



45. Second, he opines that a first order increase would not include "large peak-to-trough variations in blood plasma levels." (*Id.* at ¶ 22.)

46. Third, he opines that a first order increase would not include "alternating periods of significantly faster or slower increases." (*Id.*)

47. Fourth, he opines that "[f]irst-order absorption is characterized by a rate of drug absorption that depends on and is proportional to the concentration of the drug available." (Fleckenstein Decl. ¶ 21.) This is the equation I discussed above.

48. I do not believe these definitions would allow a POSA to understand the boundaries of the claimed invention with reasonable certainty. This is so for at least four reasons.

49. The *first* problem with Dr. Fleckenstein's definitions is that both Figure 1 and the equation are inconsistent with the plain meaning of the word "steadily." A POSA would

understand a "steady" increase to be a *constant* increase. For instance, one dictionary sets out the first definition of steady as "[f]irm in position or place; stable," and notes that synonyms include "even, equable, uniform, and constant." THE AMERICAN HERITAGE DICTIONARY 1192 (2d College ed. 1991) (JA232). Another dictionary sets out the first three definitions of "steady" as: "1. Firmly placed or fixed; stable in position or equilibrium . . . 2. Even or regular in movement . . . 3. Free form change, variation, or interruption; uniform; continuous . . . . constant, regular, or habitual." Synonyms include "balanced," "undeviating," and "invariable." RANDOM HOUSE WEBSTER'S UNABRIDGED DICTIONARY 1863 (2d ed. 2001) (JA235). In other words, the *rate* of increase would be *constant* over time.

50. The equation, by contrast, shows that due to depletion of the drug over time, the rate of delivery will decline. In other words, the *rate decreases* over time.

51. The data reflected in Figure 1 demonstrate that mean plasma concentration levels fluctuate over time; they do not increase "steadily." Table 1 of the patents, which is reproduced below, shows the data of Figure 1 and makes this clear. The actual mean plasma concentration levels do not increase over every individual reported time period (for example, the reported mean plasma level concentration decreases from 42 to 48 hours).

TABLE 1

HOURS[1]	MEAN[2]	STD. DEV.[3]	CV %[4]
6	1.76	6.20	352.77
12	18.47	26.00	140.78
18	37.45	36.16	91.67
24	58.94	44.66	75.76
30	67.69	48.78	72.06
36	82.44	53.02	64.32
42	107.61	65.43	60.81
48	104.69	60.69	57.97
54	105.81	66.68	63.02
60	112.93	63.02	55.81
66	129.25	64.37	49.80
72	130.55	64.16	49.14
78	122.83	54.97	44.75
84	129.03	51.50	39.92
90	139.50	68.26	48.93
96	146.70	62.76	42.78
102	130.19	57.68	44.31
108	135.49	67.72	49.98
114	150.24	71.69	47.72
120	136.22	63.62	46.70
126	130.25	57.77	44.35
132	124.78	52.82	42.34
138	138.55	58.34	42.11
144	115.23	48.30	41.92
150	116.30	49.04	42.16
156	120.07	50.88	42.38
162	117.66	52.71	44.80
168	102.00	49.92	48.94

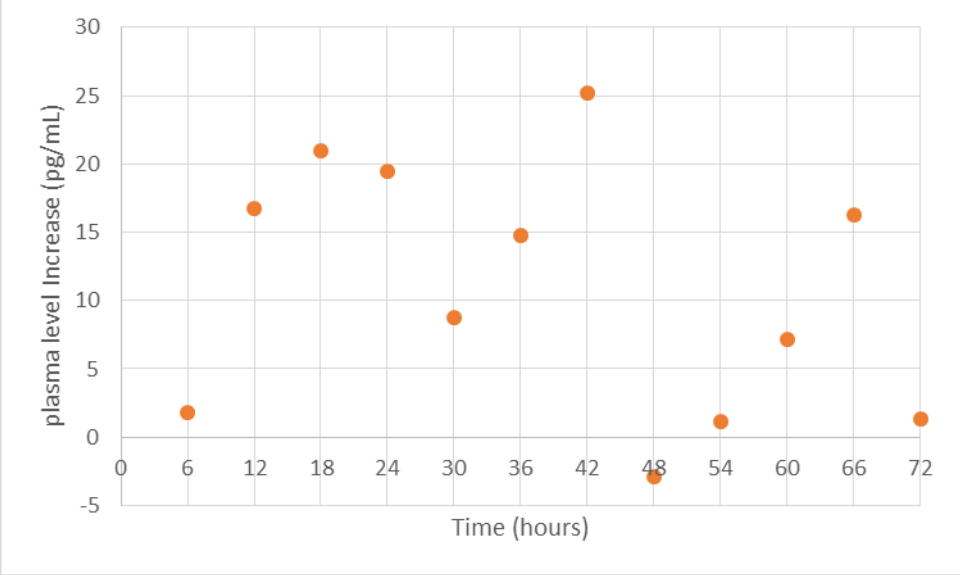
(JA39, RE ’408 patent, 25:30-60.)

52. Using the data from Table 1 of the patent, the increase in mean plasma level can be determined for each six-hour time interval from zero to 72 hours. Those results are shown in Table A.

Time (hr)	Mean (pg/mL)	Plasma Level Increase (pg/mL)
0	0	
6	1.76	1.76
12	18.47	16.71
18	39.45	20.98
24	58.94	19.49
30	67.69	8.75
36	82.44	14.75
42	107.61	25.17
48	104.69	-2.92

Time (hr)	Mean (pg/mL)	Plasma Level Increase (pg/mL)
54	105.81	1.12
60	112.93	7.12
66	129.25	16.32
72	130.55	1.3

Table A: The change in plasma level over each six-hour interval using the data in Table 1 of the patent



A graphical representation of the plasma level increase values from Table A

53. These results show that the plasma level increase varies substantially over the 72-hour time period. It is certainly not constant. Note in particular, that from 42 to 48 hours the plasma level *decreases*. Hence, the plasma level does not steadily increase from 0 to 72 hours, and in fact, actually does not increase at all over some time intervals.

54. The *second* problem with Dr. Fleckenstein's definitions is that the third definition—absence of "alternating periods of significantly faster or slower increase"—does not describe Figure 1. As shown in Table A and the corresponding graph, the plasma level increase over six-hour periods from 0 to 72 hours, ranges from greater than 25 pg/mL to a value of -2.9

pg/mL. Thus, contrary to Dr. Fleckenstein's assertion, there are indeed "alternating periods of significantly faster or slower increase."

55. The *third* problem with Dr. Fleckenstein's definitions is that the first-order equation does not describe Figure 1. As I explained, the equation requires that the rate of absorption decrease over time, because the amount of drug available at the absorption site necessarily decreases as it is absorbed. But as the results in Table A and the corresponding graph (derived from Figure 1) show, the rate of absorption is clearly increasing initially, only to decrease later before increasing and decreasing again. This is not the behavior described in the equation, and clearly shows the fluctuations seen in clinical data.

56. The *fourth* problem with Dr. Fleckenstein's definitions is that the second and third definitions are purely subjective. What is a "large" peak-to-trough variation according to Dr. Fleckenstein? What are "significantly" faster or slower increases, according to Dr. Fleckenstein? A POSA would not know. According to these standards, the only way to tell if the term is met is to have Dr. Fleckenstein tell you. I do not believe this is an appropriate standard because it cannot be applied in an objective manner.

57. Thus, for these reasons, I believe that a POSA would not be able to understand the boundaries of the claimed invention with reasonable certainty. As I understand the law, this means the construction would be indefinite.

B. Dr. Fleckenstein's arguments in support of his construction show that "steadily" is indefinite.

58. In my opinion, some of the arguments advanced by Dr. Fleckenstein in support of his proposed construction actually demonstrate the weakness of that construction.

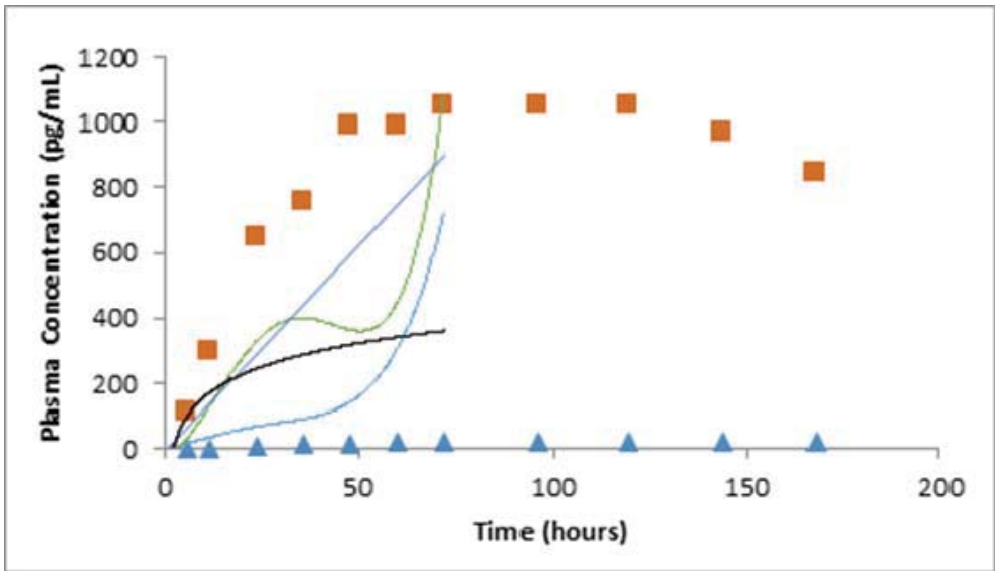
59. Dr. Fleckenstein never gives a single definition of "steadily" that could be objectively applied. Instead, to tell whether the claims are met under his proposal, one would have to rely on his subjective judgment alone.

60. Dr. Fleckenstein makes several comments about the clinical benefits of a "steady" plasma increase that may well be true, depending on what "steady" actually means to him, but they are equally true of an increase over time even with fluctuations in the concentrations and rates. For instance, Dr. Fleckenstein states that a steady plasma increase "would be a desirable property for a transdermal dosage form" used for "prolonged and effective pain management." (Fleckenstein Decl. ¶ 25.) But an increase over time, even with fluctuations, will share the same property in my opinion.

61. Dr. Fleckenstein also argues that his construction avoids large peaks and troughs in blood concentration, which has clinical benefits. (*Id.*) Perhaps, but this is not described in the patent and is purely subjective. A diminishing increase described by the equation would have the same properties, although a transdermal patch applied to an actual patient will never provide data that will match the equation precisely. And as I explained above, the very point of the "first order" term was to distinguish the sharp, stepwise increases associated with injection.

62. Dr. Fleckenstein further argues that "[a]ll of the claims [of the patents-in-suit] that specify particular blood plasma profiles over the course of administration also specify steadily increasing blood plasma concentration ranges." (Fleckenstein Decl. ¶ 24.) But while it is true that the upper and lower bounds of the plasma level concentrations claimed do increase during the period from administration through 72 hours (see, for example, RE '571 patent claim 1), the broad range of concentrations claimed encompass an infinite number of possible plasma profiles. In particular, the claimed ranges encompass an infinite number of possible types of increase.

The below graph depicts the upper bound (squares) and lower bound (triangles) of the plasma level concentrations recited in claim 1 of the RE '571 patent. The various lines reflect plasma concentration increases within the claimed bounds. But it is not clear which, if any, of these lines reflect an increase that is "steady," according to Dr. Fleckenstein.



63. Thus, for these reasons, I believe that a POSA would not be able to understand the boundaries of the claimed invention with reasonable certainty. As I understand the law, this means that the construction would be indefinite.

64. Simply put, Dr. Fleckenstein's arguments do not give any discernible meaning to the term "steadily." For that reason, the term would render the claims indefinite, and thus should not be used to define "first order."

65. Instead, my opinion is that the term "first order plasma level increase" means "plasma concentrations which increase over a specified time period."

IX. ADDITIONAL INFORMATION

66. My fee for my work in this case is $600 per hour. No part of my fee is contingent on the outcome of this case, or contingent on the substance of any of my opinions.

67. A listing of the cases in which I have testified as an expert in a deposition or at trial within the past four years is attached hereto as Appendix B.

68. I reserve the right to prepare exhibits to summarize or support the opinions and bases set forth above.

Date: October 9, 2015

Russell Owen Potts, Ph.D.